recurrent torsion and in those cases undergoing spontaneous detorsion, we believe that bilateral orchidopexy is advisable.

SUMMARY

1. Torsion is more common than the number of reported cases would indicate.

2. Early diagnosis and treatment are necessary to save the testicle.

3. Early and helpful diagnostic signs, not previously emphasized, are:

(a) early edema of the scrotal skin, sharply limited to the side of the torsion and extending up to the side of the twist;

(b) the epididymis cannot be palpated separately from the testis or occupy an abnormal position if palpable.

4. The most effective treatment is early surgery.

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SULFONAMIDE COMPOUNDS: BLOOD CHANGES THEREFROM*

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ATTENTION has repeatedly been directed to the blood changes that occur during sulfonamide therapy, and new types of reactions are reported periodically. Nevertheless, the relative frequency and significance of the blood reactions remain unsettled. It is of utmost importance that the medical profession know what time during therapy reactions appear, how long during and after treatment the blood count must be checked, what group of patients is most likely to be affected, and which sulfonamide compound is most apt to produce blood changes.

In order to clarify these subjects, we have attempted to correlate previous reports and check them against a series of patients treated at the Los Angeles County General Hospital during 1940. In this study we have found certain unfamiliar facts which we believe are worthy of emphasis.

* Read before the Section on Medicine at the Seventieth Annual Session of the California Medical Association, Del Monte, May 5-8, 1941.

SELECTION OF MATERIALS

The case histories of 540 patients who had received one or more of the sulfonamide compounds during 1940 were reviewed. Only those patients who received medication for 36 hours or more, who had blood counts shortly before or after treatment was started and at later intervals, were selected for study. In each case, one or more blood concentrations had been recorded during therapy.

Since there was so much diversity in the diseases treated and in the hospital departments concerned, observations on cyanosis and blood chemistries were not made regularly, and can not, therefore, be used in any statistical sense.

TABE I.—*Incidence of Anemia (Per Cent)*

Drug	10-20%	20-30%	30+ %	Total Per Cent
Sulfanilamide	21	10	4	35
Sulfapyridine	24	10	4	38
Sulfathiazole	27	3	0	30
Mixed Group	34	16	9	59
TOTALS	24	11	5	40

TABLE II.—*Incidence of Anemia—Children and Adults Expressed in Per Cent*

Drug	Age	10-20%	20-30%	30+ %
Sulfanilamide	A	25	12.5	3.8
	C	15	0	10
Sulfapyridine	A	23	12	2.6
	C	20	0	5.5
Sulfathiazole	A	16	4	0
	C	50	0	0
Mixed Groups	A	36.5	17.4	9.5
	C	0	25	0

A = Adults
C = Infant or Child

TABLE III.—*Hemolytic Anemias*

Drug	Total Cases	Mild	Sub-Acute	Acute	Cases	%
Sulfanilamide	133	3	2	1	6	4.5
Sulfapyridine	196	2	1	2	5	2.5
Sulfathiazole	37	1	0	0	1	2.7
Mixed Group	67	1	5	1	7	10.4
TOTALS	433	7	8	4	19	4.3

There being no practical method by which degree of illness can be determined, no such effort was made. When there was a question as to whether the blood changes were due to the disease or to the drug, the case was placed in the "no reaction" group.

Blood counts were considered adequate when they included hemoglobin percentage, and/or red cell count and leukocyte count. Differential white cell counts were frequently recorded.

The 433 cases retained in this series were studied particularly as regards the type of drug used, days of treatment, maximum blood concentration, age, sex, race and changes in the blood picture. Particular attention was given to the day of treatment on which changes in the blood occurred, the rapidity of the change and the outcome.

DISTRIBUTION OF CASES

Of the 433 patients in the series, 133 received sulfanilamide, 196 sulfapyridine, 37 sulfathiazole and 67 received more than one of these compounds. The total number of males somewhat exceeded the number of females, there being 230 of the former and 203 of the latter. There were 72 infants and children, 361 adults; all ages ranging from new born infants to 110 years. Treatment extended from 36 hours to 65 days. Included were 392 Caucasians (including Mexicans), 37 negroes and 4 Asiatics.

FINDINGS

Effects upon the Hemoglobin and Red Blood Cells:

In the entire series an anemia of 10-20 per cent occurred in 110 patients (24 per cent). Forty-six patients (11 per cent) dropped 20-30 per cent, and 19 (5.0 per cent) developed an anemia of 30 per cent. Thus, 40 per cent of all patients (Table I) developed some degree of anemia. There was relatively little difference in the occurrence of mild anemias from sulfanilamide, sulfrapyridine or sulfathiazole but the incidence was considerably higher in the group of patients who received more than one of these compounds. Of the 60 per cent of patients who developed no anemia, 21 per cent actually showed an increase in hemoglobin or the red cell count.

Infants and children treated with sulfanilamide and sulfapyridine developed severe anemia more often than adults. (Table 2.) Fifty per cent of infants and children who received sulfathiazole developed mild progressive anemia, but none showed severe or moderately severe changes. Likewise there were distinctly fewer cases of severe or moderately severe anemias in patients of all ages treated with sulfathiazole than in those who received sulfanilamide or sulfapyridine.

There were 19 patients who developed hemolytic anemia, an incidence of 4.3 per cent (Table 3.) Seven were mild, 8 subacute and 4 acute. The relative number was greatest with sulfanilamide and combined therapy, but hemolytic anemia occurred with each drug used. One patient, who developed acute hemolytic anemia during sulfapyridine therapy for pneumonia, died. Four of the 19 hemolytic anemias occurred in negroes. Figures 1-4 are typical examples of the anemias.

DISTURBANCE OF THE WHITE BLOOD CELLS

There were 10 patients who developed depression of the white blood cells. Six were leukopenias, the counts ranging from 4050 to 3100, all of whom recovered after the drugs were discontinued. One leukopenia appeared after 36 hours of sulfapyridine. Four patients (0.92 per cent) developed agranulocytosis, two of whom died: two had received sulfanilamide, one sulfapyridine and one sulfathiazole. Three of the four patients had received fairly large doses, the agranulocytosis appearing after 15 and 17 days of treatment (Fig. 5). However, one patient (not included in the chart because all blood counts were not available) had received 33 grams of sulfanilamide in 8.5 days from an outside physician. Three days after discontinuing sulfanilamide he developed fever, sore throat and furuncles. He was admitted four days later with an absolute agranulocytosis and 950 white cells. He died three days after admission.

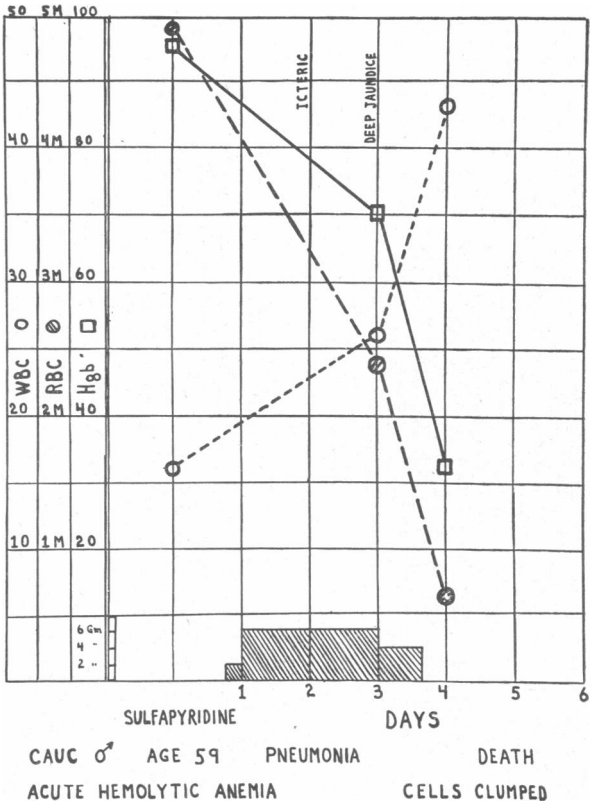

Chart 1.—Acute hemolytic anemia due to sulfapyridine.

A 34-year-old Mexican male received 94 grams of sulfanilamide in 15 days, at which time the white count was 8200. Three days later he developed fever and pain in the ears, was given 14 grams of sulfanilamide in the next two days, after which the white count was found to be 300. He recovered.

A 48-year-old white man received 64 grams of sulfathiazole in 9 days and 45 grams in 8 days. The drug was stopped after the first course because of a rash, but was resumed two days later. He received treatment two days after the leukocyte count was 4000, no further count being made for five days, at which time there was an absolute agranulocytosis of 1200 cells. He recovered from the neutropenia, but later died of the endocarditis for which he was being treated.

A 54-year-old white man received 46 grams of sulfapyridine in 8 days, and a second course of 28 grams in 7 days. On the last day of treatment there were 8000 leukocytes. Six days later he developed high unexplained fever, and on the

9th day, after sulfapyridine was discontinued, the white blood count was found to be 1200 with an absence of neutrophils. He died in spite of improvement in the white count.

COMMENT

Most authors who have reported anemia due to sulfonamide therapy have failed to give the criteria by which cases are selected. This is confusing, and probably accounts for discrepancies which occur in various statistics. Since all sulfonamide anemias are actually hemolytic [1, 2, 3], it is important that they be divided into groups

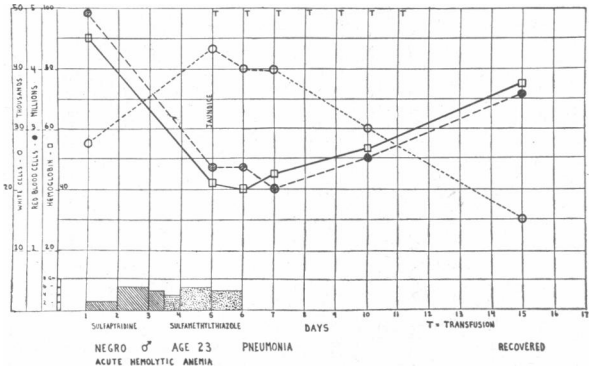

Chart 2.—Acute hemolytic anemia due to sulfapyradine and sulfamethylthiazole.

which serve to distinguish them. Arbitrarily we have not included as hemolytic any slowly progressive anemia, even though the ultimate decrease in hemoglobin or red cells was marked, for this type of anemia is probably no contraindication to continued therapy. The following classification was used:

1. Mild hemolytic anemia: A decrease in hemoglobin or red cell count of 25 per cent or more in 7 days or less.

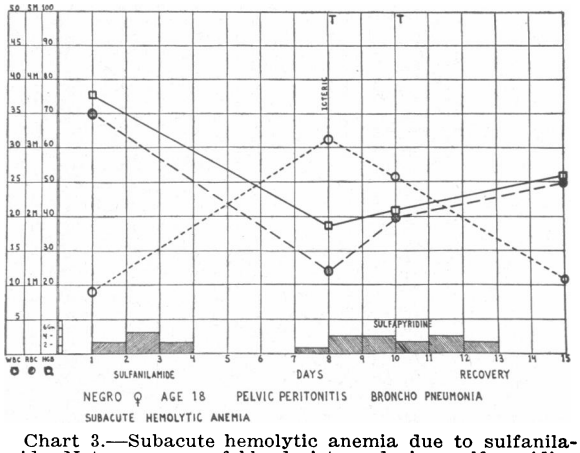

Chart 3.—Subacute hemolytic anemia due to sulfanilamide. Note recovery of blood picture during sulfapyridine administration.

2. Subacute hemolytic anemia: An anemia of at least 30 per cent, developing in less than 10 days and accompanied by bilirubinemia.

3. Acute hemolytic anemia: A sudden or rapidly developing anemia of at least 30 per cent, accompanied by fever, bilirubinemia, leukocytosis and increased immature red cells.

It is difficult to explain the fact that all age groups developed mild as well as severe anemia more often when they received more than one of the sulfonamide drugs, than when only one compound was given. In many of the cases there was a period of several days between the cessation of one drug and the introduction of another. Specific sensitivity is known to occur [4, 5, 6], and patients who develop sensitivity to one compound often react unfavorably to closely related substances. But there were numerous patients who reacted unfavorably to one compound, yet tolerated another. I am inclined to believe that often the drug was changed because of poor response, and that some of the apparent failure to respond was in reality an unrecognized early drug reaction.

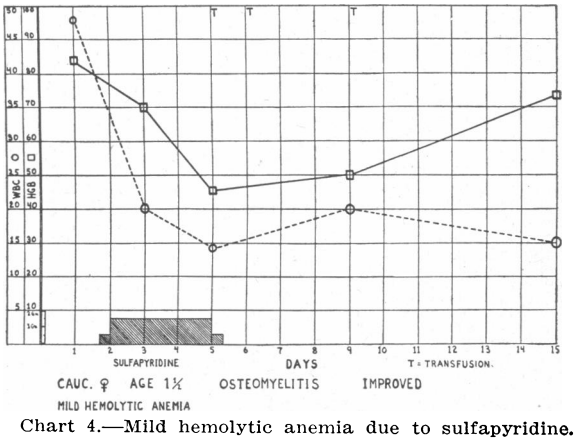

Chart 4.—Mild hemolytic anemia due to sulfapyridine.

At first glance, the total dose received and the duration of treatment appeared slightly greater in adults who developed anemia than in those who did not. But when each drug series was broken down into groups according to total dose received and days of treatment, a very significant fact was discovered. Whenever 10 grams or more of sulfanilamide were given, whether in 3 days or in 20 days, the number and severity of anemias was the same. Regardless of whether relatively small doses of sulfapyridine were given in a few days or larger doses were given in the same number of days or over a longer period, the incidence of anemias was the same.

While it is true that the majority of hemolytic anemias develop during the first 3-4 days of treatment, they not infrequently develop much later. One patient who received sulfanilamide had shown a steady gain in hemoglobin up to the tenth day of treatment and then dropped 32 per cent between the tenth and fourteenth days. Another patient, treated with sulfathiazole, showed no increase in anemia until the twelfth day of

treatment, then dropped 22 per cent in the next 3 days in spite of frequent transfusions. Although Spink and Hansen[8] report a case of moderate anemia from sulfathiazole, this is the first case we have found which developed a rapid anemia. In 3 patients, it is noteworthy that the onset of gradual anemia did not occur until the eleventh, thirteenth and fourteenth days of treatment.

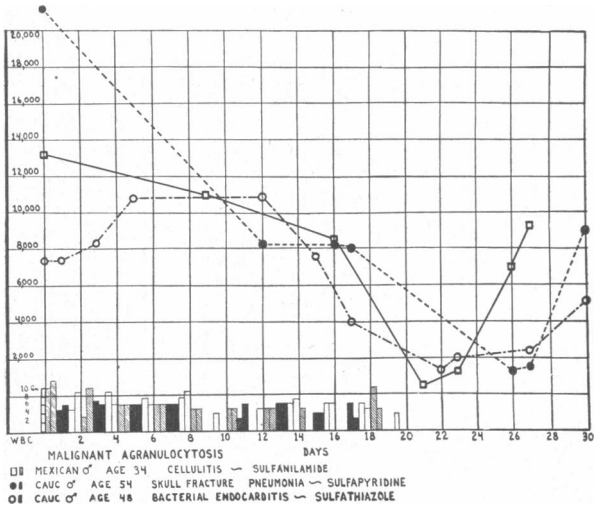

Chart 5.—Malignant agranulocytosis in 3 cases treated with sulfanilamide, sulfapyridine and sulfathiazole.

It has been said that sulfonamide hemolytic anemia occurs less frequently in negroes than in Caucasians, but I have been impressed by the number of negro patients who have appeared in reports[4, 9, 10]. In the present series there were 37 negroes (Fig. 6), 10.8 per cent of whom developed hemolytic anemia as compared with an incidence of 3.9 per cent for Caucasians. No sickling was found.

Sulfonamide anemia apparently differs from familial hemolytic anemia, secondary macrocytic anemia and anemia produced by specific hemolysins. There is a tendency toward macrocytic hypochromic anemia with reduced mean corpuscular hemoglobin concentration,[1] no tendency toward spherocytosis, and no change in the resistence to hypotonic salt solution.[11] The red-cell fragility in cases of sulfonamide hemolytic anemia in our series, and in those reported elsewhere[4, 9, 10, 11, 12, 13], have been normal.

Fatal thrombocytopenia from sulfapyridine has been reported[14] and acute hemolytic anemia with autoagglutination is known to occur.[12] One patient in our series who had received 27 grams of sulfapyridine in 3.5 days developed acute hemolytic anemia. Suitable donors could not be found because of persistent late clumping of the cells, autoagglutination having perhaps been present.

It has been generally understood that one no longer need fear toxic effects after sulfonamide compounds have been discontinued. This conception should be corrected, for there is ample proof that reactions, hemolytic anemia or rapid diminution in the white cell count may occur after withdrawal of the drug[7, 13, 15, 16, 17, 18, 19, 20]. The patient who developed agranulocytosis 9 days after sulfapyridine had been discontinued, is a good example.

Last year Long, et al[21] reported that they knew of no deaths from disturbance of the white cells during the first 12 days of therapy with any of the sulfonamide drugs. We herein have reported an agranulocytic death which followed 33 grams of sulfanilamide in 8.5 days. Spain[18] reported a fatal case of granulocytopenia that occurred after only 4.5 grams each of sulfanilamide and sulfapyridine were given in 4 days.

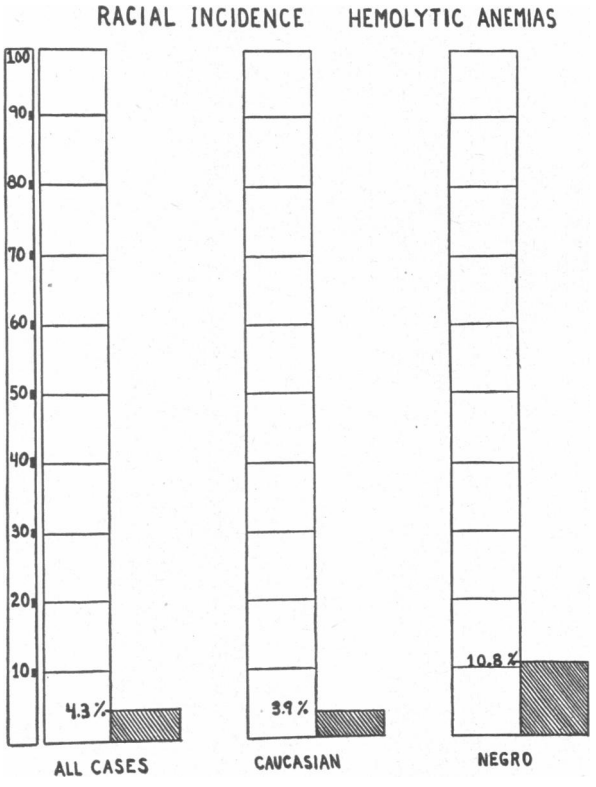

Chart 6.—Comparison of hemolytic anemia incidence in Caucasian and Negro patients.

The first agranulocytic death attributed to sulfathiazole has recently been reported by Kennedy and Finland.[22] The patient in the present series who developed agranulocytosis from sulfathiazole is the third such case reported. Thus far sulfathiazole reports are too few to be of comparative value; however, it is important to know that the same reactions occur with each of the sulfonamide compounds.

In spite of a recent statement[21] that physicians are over cautious in using sulfonamide compounds, I am of an opposite opinion. When used properly all of these drugs have a definite and invaluable place in the treatment of disease. Since

severe anemias and leukopenias occur late and early during therapy, routine blood counts must be made every two or three days during the entire course of treatment with any of the sulfonamide compounds. Patients should be kept under surveillance at least 10 days after treatment has been discontinued, or instructed to report the first sign of abnormal reaction, for the cessation of therapy is no insurance of safety.

SUMMARY AND CONCLUSIONS

Forty per cent of 433 patients receiving one or more of the sulfonamide compounds developed mild to severe anemia. The percentage of total anemias was about the same for sulfanilamide, sulfapyridine and sulfathiazole, but was considerably greater when more than one of these compounds were used.

Infants and children who received sulfanilamide or sulfapyridine were more susceptible to severe anemia than were adults. Although fifty per cent of infants and children treated with sulfathiazole developed mild anemia, none developed severe or moderately severe changes. In all age groups, severe or even moderately severe anemia occurred less frequently with sulfathiazole than with sulfanilamide or sulfapyridine.

Hemolytic anemia developed in 4.3 per cent of patients with one fatality. Each drug was responsible for hemolytic anemia, but sulfanilamide and mixed therapy provided the highest incidence. Negroes developed hemolytic anemia almost three times as frequently as Caucasians. Rapidly developing anemias occurred as late as the tenth and twelfth days of treatment; the onset of gradual anemias appeared as late as the eleventh, thirteenth and fourteenth days.

The number and severity of anemias were not dependent upon the total dose received, the duration of treatment or the blood concentration. Therefore, the administration of small doses over a longer period of time is no insurance against anemia.

Two and three-tenths per cent of patients developed leukopenia, four (0.92 per cent) proceeding to agranulocytosis with two fatalities. Three had received sulfanilamide, sulfapyridine or sulfathiazole for 15 and 17 days, but the fourth patient died following 33 grams of sulfanilamide in 8.5 days. The sulfapyridine fatality had a normal leukocyte count on the last day of treatment and developed agranulocytosis 9 days later. Six similar cases have been reported previously.

Routine blood counts must be made every two to three days during the entire course of treatment with any of the sulfonamide compounds. Since reactions may occur after cessation of therapy, patients should be kept under surveillance after treatment has been discontinued.

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MEDICAL EPONYM

Kahn Test

The precipitation test for syphilis that has attained the widest use in this country is that proposed by R. L. Kahn (b. 1887), of the Michigan Department of Health, in his paper, "Simple Quantitative Precipitation Reaction for Syphilis," which appeared in the *Archives of Dermatology and Syphilology* (5:570-578, 1922). The author's test has been modified and discussion of it amplified in numerous later papers and a book.

> The precipitation method proposed in this paper is based on the employment of syphilitic serum with alcoholic extract antigens of heart muscle. In this regard it is similar to the precipitation reactions of Meinicke, Sachs and Georgi, and Dreyer and Ward. . . . The test proposed however, differs from each of these reactions in essential phases.—R. W. B., in *New England Journal of Medicine.*

MEDICAL EPONYM

Huntington's Chorea

George Huntington (1850-1916), of Pomeroy, Ohio, read an essay before the Meigs and Mason Academy of Medicine, Middleport, Ohio, on February 15, 1872, "On Chorea," which was published in the *Medical and Surgical Reporter* (26:317-321, 1872).

> And now I wish to draw your attention more particularly to a form of the disease which exists, so far as I know, almost exclusively on the east end of Long Island, . . . Chorea, as it is commonly known, . . . is of exceedingly rare occurrence there.
>
> The hereditary chorea, as I shall call it, is confined to certain and fortunately a few families. . . . It is attended generally by all the symptoms of common chorea, only in an aggravated degree hardly ever manifesting itself until adult or middle life; and then coming on gradually but surely, increasing by degrees, and often occupying years in its development, until the hapless sufferer is but a quivering wreck of his former self.—R. W. B., in *New England Journal of Medicine.*

A sound mind in a sound body, is a short but full description of a happy state in this world. He that has these two, has little more to wish for; and he that wants either of them, will be little the better for anything else. John Locke, *Some Thoughts Concerning Education.*